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MARSHALL, GERSTEIN & BORUN LLP 6300 SEARS TOWER 233 S. WACKER DRIVE CHICAGO, IL 60606			HUYNH, PHUONG N	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/046,922

Applicant(s)

ALITALO ET AL.

Examiner

Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-74 is/are pending in the application.
- 4a) Of the above claim(s) 14-20 and 39-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 21-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

1. Claims 1-74 are pending.
2. Applicant's election with traverse of Group I, Claims 1-38 (now claims 1-13 and 21-38) drawn to a specific isolated peptide, a peptide dimer comprising first and second peptide monomer wherein the first and second peptide monomers comprises the same peptide and a composition comprising said peptide that read on species SEQ ID NO: 35, filed 3/8/04, is acknowledged. The traversal is on the grounds that all of the claims of group II recite as an element, a peptide of Group I. The examiner has not and cannot point to any art that the examiner would search for group I or Group II that would not also be relevant to the other group. It is impossible for a monomer to be unrelated to a heterodimer when the heterodimer must include as a component the monomer. Groups 3-6 all pertain to an invention defined by claims 39-43. It is impossible for a method defined by a single to be unrelated to itself. The relatedness of a peptide and a nucleotide sequence that encodes it is self evident in Groups 3-10. As to Groups 11-16, all of the method claims pertain to methods of screening or imaging. They all involved the steps of contacting biological material with a composition comprising a peptide of the invention. There would be no burden in examining all of these claims together. Even with independent and distinct inventions, the MPEP instructs that an examiner should only restrict the inventions if examination of inventions together would pose serious burden. No such burden has been demonstrated here.

This is not found persuasive because of the reasons set forth in the restriction mailed 1/5/04. The claims of Group 2 are drawn to dimeric peptide comprising a first and second peptide monomer wherein the first and second peptides are different. A search of Group 2 would not encompass the claims of Group 1 as evident by different class and subclass. Further, the DNA and protein databases have grown in size, exponentially since the publication of the Official Gazette Notice in 1996. What was once a relative simple search has now become far more burdensome, due both to performing the computer search and the analysis of the search results. The sequence search and literature search, both particularly relevant to this art, is not coextensive and is much more important in evaluating the burden of search. A search of Group I would not necessary identified prior art relevant to the examination of Group II.

Inventions of Groups 3-16 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation,

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different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the methods of inhibiting the proliferation of cells, the method of treating distinct disease, the method of screening, imaging using distinct products such as peptide and nucleic acid differs with respect to their structure, method steps and therapeutic endpoints as evident by different class and subclass. Therefore, they are patentably distinct. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Upon reconsideration, the search has been extended to include peptides of SEQ ID NO: 32-33, 34, 67 and 68. Therefore, the requirement of Group I (now claims 1-13 and 21-38) drawn to a specific isolated peptide, a peptide dimer comprising first and second peptide monomer wherein the first and second peptide monomers comprises the same peptide and a composition comprising said peptides of SEQ ID NO: 32-35, 67 and 68 and Groups 2-16 is still deemed proper and is therefore made FINAL.

3. Claims 14-20 and 39-74 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 1-13 and 21-38 drawn to a specific isolated peptide, a peptide dimer comprising first and second peptide monomer wherein the first and second peptide monomers comprises the same peptide and a composition comprising said peptide of SEQ ID NO: 32-35, 67 and 68 are being acted upon in this Office Action.
5. Claims 2-3, 12, 22-29, 31-32, and 35-36 are objected to because "A" should have been "The" for all dependent claims.
6. Claims 5-11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).
7. Claim 9 is object to because claim 9 cannot depend on itself.
8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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9. Claims 1-13 and 21-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated peptide consisting of the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ wherein X_1 is G, X_2 is Y, X_3 is W, X_4 is L, X_5 is T, X_6 is I, X_7 is W and X_8 is G as set forth in SEQ ID NO: 35 wherein said peptide binds to VEGFR-3 and inhibiting the binding of VEGF-C from binding to VEGFR-3, the said peptide further comprises of amino and carboxy-terminal cysteine residues, a peptide dimer comprising a first and second peptide wherein the first and second peptide are SEQ ID NO: 35, a composition comprising the peptide consisting of an amino acid sequence of SEQ ID NO: 35 or a peptide dimer comprising a first and second peptide wherein the first and second peptide are SEQ ID NO: 35 and a pharmaceutically acceptable carrier for imaging or screening assay, **does not** reasonably provide enablement for all isolated peptide "comprising" the formula as set forth in claim 1 and wherein the amino acid residue at $X_1X_2X_3X_4X_5X_6X_7$ or X_8 is conservatively substituted thereof (claims 1, 4-12), *any* isolated peptide "comprising" Y1GYWLTIWGY2 wherein Y1 and Y2 are any amino acids, *any* peptide "comprising" CGYWLTIWGC, *any* isolated peptide GYWX1,X2X3W (SEQ ID NO: 67) wherein X1, X2 and X3 comprise any amino acids and wherein the peptide binds VEGFR-3, *any* isolated peptide "comprising" the amino acid sequence GYWX1X2X3WX4 wherein X4 comprises any amino acid, *all* isolated peptide mentioned above further comprising amino- and carboxy-terminal cytosine residues for treating any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a peptide consisting of the amino acid sequence GYWLTIWG of SEQ ID NO: 35 that binds to VEGFR-3 and inhibiting the binding of VEGF-C from binding to VEGFR-3. The said peptide further comprises amino and carboxy terminal cysteine residues. The specification further discloses a peptide dimer comprising a first and

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second peptide wherein the first and second peptides are the same comprising SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or screening assays.

The specification does not teach how to make all isolated peptide (claims 1-13, 21-38) mentioned above because the term “comprising” is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added and whether the resulting peptide maintains its structure and function. Further, binding is not equivalent to inhibiting VEGF-C function. A peptide may bind to VEGFR-3 but does not necessarily mean binding equal to inhibiting VEGF-C mediated function. Given the indefinite number of undisclosed peptide, it is unpredictable which undisclosed peptide having various conservative and non-conservative substitution would maintain its structure, let alone having competitive inhibition of VEGF-C/D binding to VEGFR-3. The specification discloses conservative substitution as a substitution of one amino acid for another amino acid that has similar properties as shown in Table C and retains its properties of being a competitive inhibitor of VEGF-C binding to VEGFR-3. However, claims 4-11 as written having amino acid substitution that is non-conservative substitution instead of conservative substitution. A conservative substitution for glycine residue (X₁) in claim 4, wherein glycine is aliphatic non-polar amino acid, should have been either alanine or proline. A conservative substitution for tyrosine residue (X₂) in claim 5 should have been Trp, Phe, Thr or Ser. A conservative substitution for tryptophan residue (X₃) in claim 6 should have been Tyr. A conservative substitution for leucine (X₄) in claim 7 should have been Ile, Val, Met, Ala, or Phe. A conservative substitution for threonine residue (X₅) in claim 8 should have been Ser. A conservative substitution for isoleucine residue (X₆) in claim 9 should have been Leu, Val, Met, Ala, or Phe. A conservative substitution for tryptophan residue (X₇) in claim 10 should have been Tyr. A conservative substitution for glycine residue (X₈) in claim 11 should have been Pro or alanine. Further, there is insufficient working examples demonstrating that all undisclosed peptides having various amino acid substitution still bind to VEGFR-3 and competitively inhibit the binding of VEGF-C from binding, in turn, would be useful for treating cancer.

With regard to claim 21, there is insufficient guidance and working example as to what is the amino acids for X₁, X₂ and X₃ in SEQ ID NO: 67. Likewise, there is insufficient guidance and working example for the amino acids for X₁, X₂, X₃ and X₄ in SEQ ID NO: 68 (Claim 22).

Further the term "comprises" is open-ended. It expands the peptide of SEQ ID NO: 68 to infinity.

With regard to claim 30, in addition to the problem of undisclosed peptide mentioned above, there is insufficient guidance as to the "therapeutic protein amino acid sequence" without the amino acid sequence, let alone which undisclosed amino acid sequence is therapeutic.

With regard to claim 31, in addition to the problem of undisclosed peptide and therapeutic protein amino acid sequence mentioned above, the chimeric protein now "comprises" a tumor necrosis factor.

With regard to claim 32, there is insufficient guidance as to the binding specificity of all antibody or fragment thereof.

With regard to claim 33, there is insufficient guidance as to which particular "modification" that would increase the circulating in-vivo half-life of the undisclosed peptide.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Attwood *et al* teaches that protein function is context-dependent; the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable and knowing structure alone will not inherently tell us function (See figure, entire document).

Given the lack of amino acid sequences for all undisclosed peptide, it follows that any undisclosed peptide further comprises amino and carboxyl terminal cysteine residues are not enabled. It also follows that any undisclosed peptide that forms intramolecular bond or disulfide bonds between cysteine residues are not enabled. It stands to reason that any cytotoxic agent, radioisotope, anti-neoplastic prodrug, chimeric protein, composition and dimer comprising the undisclosed peptide are not enabled.

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For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-13 and 21-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for all isolated peptide “comprising” the formula as set forth in claim 1 and wherein the amino acid residue at $X_1X_2X_3X_4X_5X_6X_7$ or X_8 is conservatively substituted thereof (claims 1, 4-12), *any* isolated peptide “comprising” Y1GYWLTIWGY2 wherein Y1 and Y2 are any amino acids, *any* peptide “comprising” CGYWLTIWGC, *any* isolated peptide GYWX₁X₂X₃W (SEQ ID NO: 67) wherein X₁, X₂ and X₃ comprise any amino acids and wherein the peptide binds VEGFR-3, *any* isolated peptide “comprising” the amino acid sequence GYWX₁X₂X₃WX₄ wherein X₄ comprises any amino acid, *any* isolated peptide mentioned above further comprising amino- and carboxy-terminal cytosine residues, *any* chimeric protein comprising any therapeutic amino acid sequence attached to the amino acid sequence of all undisclosed peptide, *any* peptide mentioned above attached to any antibody or fragment thereof, *any* peptide mentioned above further comprises a “modification” to increase the circulating in-vivo half-life, *any* peptide dimer comprising any first and second peptide monomers comprises the same peptide mentioned above, and *any* composition comprising all isolated peptide mentioned above.

The specification discloses only a peptide consisting of the amino acid sequence GYWLTIWG of SEQ ID NO: 35 that binds to VEGFR-3 and inhibiting the binding of VEGF-C from binding to VEGFR-3. The said peptide further comprises amino and carboxy terminal cysteine residues. The specification further discloses a peptide dimer comprising a first and

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second peptide wherein the first and second peptides are the same comprising SEQ ID NO: 35. A composition comprising said peptide or dimer and a pharmaceutically acceptable carrier for imaging or screening assays.

With the exception of the specific peptide mentioned above, there is insufficient written description about the structure associated with function of all isolated peptide (claims 1-13, 21-38) mentioned above because the term “comprising” is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added and whether the resulting peptide maintains its structure and function without the amino acid sequence. The specification discloses conservative substitution as a substitution of one amino acid for another amino acid that has similar properties as shown in Table C and retains its properties of being a competitive inhibitor of VEGF-C binding to VEGFR-3. However, claims 4-11 as written having amino acid substitution that is non-conservative substitution instead of conservative substitution. A conservative substitution for glycine residue (X₁) in claim 4, wherein glycine is aliphatic non-polar amino acid, should have been either alanine or proline. A conservative substitution for tyrosine residue (X₂) in claim 5 should have been Trp, Phe, Thr or Ser. A conservative substitution for tryptophan residue (X₃) in claim 6 should have been Tyr. A conservative substitution for leucine (X₄) in claim 7 should have been Ile, Val, Met, Ala, or Phe. A conservative substitution for threonine residue (X₅) in claim 8 should have been Ser. A conservative substitution for isoleucine residue (X₆) in claim 9 should have been Leu, Val, Met, Ala, or Phe. A conservative substitution for tryptophan residue (X₇) in claim 10 should have been Tyr. A conservative substitution for glycine residue (X₈) in claim 11 should have been Pro or alanine.

With regard to claim 21, there is inadequate written description about X₁, X₂ and X₃ in SEQ ID NO: 67 without the specific amino acid residues for X₁, X₂ and X₃. Likewise, there is written description about X₁, X₂, X₃ and X₄ in SEQ ID NO: 4 without the specific amino acids for X₁, X₂, X₃ and X₄ in SEQ ID NO: 68 (Claim 22). Further the term “comprises” is open-ended. It expands the peptide of SEQ ID NO: 68 to infinity.

With regard to claim 30, in addition to the problem of the structure associated with function of the undisclosed peptide mentioned above, there is insufficient written description about the structure of the “therapeutic protein amino acid sequence” without the amino acid sequence, much less which amino acid sequence is therapeutic, and having which particular function.

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With regard to claim 31, in addition to the problem of undisclosed peptide and therapeutic protein amino acid sequence mentioned above, the chimeric protein now "comprises" a tumor necrosis factor.

With regard to claim 32, there is inadequate written description about the binding specificity of all antibody or fragment thereof.

With regard to claim 33, there is inadequate written description about which "modification" that would increase the circulating in-vivo half-life of the undisclosed peptide.

Given the lack of amino acid sequences for all undisclosed peptide, it follows that any undisclosed peptide further comprises amino and carboxyl terminal cysteine residues are not adequately described. It also follows that any undisclosed peptide that forms intramolecular bond or disulfide bonds between cysteine residues are not adequately described. It stands to reason that any cytotoxic agent, radioisotope, anti-neoplastic prodrug, chimeric protein, composition or dimer comprising the undisclosed peptides is not adequately described.

Further, the specification discloses only one specific peptide consisting of SEQ ID NO: 35 that binds to VEGFR-3 and competitively inhibits the binding of VEGF-C from binding to the VEGFR-3, the other peptides and dimer that bind to VEGFR-1, VEGFR-2m NP-1 and NP-2 are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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12. Claims 4-12, 21, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-11 as written having amino acid substitution that is non-conservative substitution instead of conservative substitution. The non-conservative substitution has no antecedent basis in base claim 1 because base claim 1 requires conservative substitution.

The "Y1GYWLTIWGY2" in claim 12 is ambiguous and indefinite because it is not clear which particular amino acid for Y1 and Y2 are part of the claimed invention. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "GYWX1X2X3W" in claim 21 is ambiguous and indefinite because it is not clear which particular amino acid(s) for X1, X2 and X3 is part of the claimed invention. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "GYWX1X2X3WX4" in claim 22 is ambiguous and indefinite because it is not clear which particular amino acid(s) in X1, X2, X3 and X4 are part of the claimed invention. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 4-5, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al* (Proc Nat. Acad. Sci USA 93: 1988-1992, March 1996; PTO 892).

Lee *et al* teach an isolated peptide such as human VRP comprising the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ wherein the amino acid residue X_1 is G, X_2 is P which is a conservative substitution of tyrosine, X_3 is H which is a conservative thereof, X_4 is K, X_5 is E which is a conservative substitution of T, X_6 is L which is a conservative substitution of I, X_7 is D which is a conservative substitution of W, and X_8 is R which is a conservative substitution of G that binds to VEGFR3 (See page 1990, Figure 1B VRP, underline in particular). The term "comprising" is

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open-ended. It expands the claimed peptide to include the reference VRP that binds to VEGFR-3. Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-11, 24-28, 30, and 32-38 are rejected under 35 U.S.C. 102(a) as being anticipated by US Pat No 6,121,416 (Sept 2000; PTO 892).

The '416 patent teaches an isolated peptide comprising the amino acid sequence such as SEEVCWPVAEWYLCNMWGR that has the formula $X_1X_2X_3X_4X_5X_6X_7X_8$ wherein the amino acid residue X_1 is W, X_2 is P, X_3 is V, X_4 is A, X_5 is E, X_6 is W, X_7 is Y and X_8 is L (See Table III, name 4D3.3, in particular). The reference amino acid sequence CWPVAEQYLC further comprises amino- and carboxy-terminal Cysteine residues C. The term "comprising" is open-ended. It expands the claimed peptide to include the reference peptide. Further, the reference amino acid residue W (X_1) is a conservative amino acid substitution of G for W (Trp) as required by claim 4. The reference amino acid residue P (X_2) is a conservative amino acid substitution of Y for P (Pro) as required by claim 5. The reference amino acid residue V (X_3) is a conservative amino acid substitution of W for V (Val) as required by claim 6. The reference amino acid residue A (X_4) is a conservative amino acid substitution of L for A (Ala) as required by claim 7. The reference amino acid residue E (X_5) is a conservative amino acid substitution of T for E (Glu) as required by claim 8. The reference amino acid residue W (X_6) is a conservative amino acid substitution of I for W (Trp) as required by claim 9. The reference amino acid residue Y (X_7) is a conservative amino acid substitution of W for Y (Tyr) as required by claim 10. The reference amino acid residue L (X_8) is a conservative amino acid substitution of G for L (Leu) as required by claim 11. Since the reference peptide has the same structure as the claimed peptide, the reference peptide inherently has the same function such as binding to VEGFR3 and inhibits VEGF-C binding to VEGFR-3 or VEGFR2. The '416 patent teaches the reference peptide forms intramolecular disulfide bond between two cysteine residues which form a cyclic peptide (See column 59, lines 45-48, column 23, line 66-67, column 24, line 31-32, in particular). The '416 patent teaches that the reference peptide can form peptide dimer comprising at least two iterated peptide sequence (Same peptide sequence) (See column 24, lines 2-5, in particular). The '416 patent teaches the reference peptide is attached to an antibody or fragment thereof (See column 27, line 52-60, column 28, line 7-8, in particular) or labeled with a radioisotope such as ^{125}I (See column 36, line 58, in particular). The '416 patent further teaches the reference peptide undergo further modification such as PEGylation to increase the circulating in vivo half-life of the

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reference peptide in a mammal (See column 29, lines 22-24, in particular). The '416 patent also teaches chimeric protein such as fusion protein comprising the reference peptide and a therapeutic protein amino acid sequence such as IgG (See column 19, lines 20-30, in particular). The '416 patent teaches a composition comprising the reference peptide and a pharmaceutically acceptable carrier such as NaCl (See column 29, line 35-65, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claims 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirohashi *et al* (Mol Pharmacol 53(6): 1068-75, June 1998 Jun; PTO 892).

Hirohashi *et al* teach an isolated peptide MLP-1 comprising the amino acid sequenceGYWISWA...that is identical to the claimed peptide comprising the amino acid sequence GYWX1X2X3W (SEQ ID NO: 67) and GYWX1X2X3WX4 (SEQ ID NO: 68) wherein X1, X2, X3 and X4 are any amino acids (See Figure 3 (A) on page 1072, amino acid residues 964-974, in particular). The term "comprising" is open-ended. It expands the claimed peptide to include the reference multi-drug resistance associated protein like protein (MLP-1). Thus, the reference teachings anticipate the claimed invention.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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19. Claims 1-11, 24-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,121,416 (Sept 2000; PTO 892) in view of US Pat No 4,975,278; PTO 892).

The teachings of the '416 patent have been discussed supra. The '416 patent teaches that reference peptide is useful as IGF antagonist for inhibiting angiogenesis in cancer (See column 25, lines 44, in particular).

The claimed invention as recited in claim 29 differs from the teachings of the reference only in that the peptide comprises an anti-neoplastic pro-drug.

The '278 patent teaches anti-neoplastic prodrug such as 5-fluorocytosine that kill tumor cells. The reference prodrug is linked to antibody via enzyme such as alkaline phosphatase, arylsulfatase, serratia protease, thermolysin, subtilisin, a carboxypeptidase, a cathepsin, D-alanylcarboxypeptidase, β -galactosidase, neuraminidase, β -lactamase, penicillin amidase or cytosine deaminase that is converted at the site of tumor to active prodrug. (claims 11-12 of '416 patent, See entire document, in particular, column 4, lines 37-67, column 5, lines 1-3). The '278 patent teaches that antibody enzyme conjugates prodrug provides enhanced selective killing of tumor cells and thus useful in the treatment of cancers (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine prodrug as taught by the '278 patent and the peptide that is useful as IGF antagonist for inhibiting angiogenesis in cancer as taught by the '416 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '416 patent teaches that reference peptide is useful as IGF antagonist for inhibiting angiogenesis in cancer (See column 25, lines 44, in particular). The '278 patent teaches anti-neoplastic prodrug such as 5-fluorocytosine kills tumor cells and that antibody enzyme conjugates prodrug provides enhanced selective killing of tumor cells and thus useful in the treatment of cancers (See abstract, in particular). *In re Kerkhoven*, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

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20. Claims 1-11, 24-26 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,121,416 (Sept 2000; PTO 892) in view of or Curnis et al (Nat Biotechnol 18(11): 1185-90; PTO 892).

The teachings of the '416 patent have been discussed supra. The '416 patent teaches that reference peptide is useful as IGF antagonist for inhibiting angiogenesis in cancer (See column 25, lines 44, in particular).

The claimed invention as recited in claim 31 differs from the teachings of the reference only in that the chimeric protein comprises a tumor necrosis factor attached to the amino acid sequence of the peptide.

Curnis *et al* teach a chimeric fusion protein such as tumor necrosis factor with a peptide such as CNGRC (NGR-TNF) (See entire document). Curnis *et al* teach clinical use of tumor necrosis factor alpha (TNF) as an anticancer drug is limited to local treatments because of its dose-limiting systemic activity. However, when TNF alpha is fused to NGR peptide, the peptide targets the TNF to the blood vessels of tumors, and is 12-15 times more efficient than TNF alone (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the peptide in the chimeric fusion protein comprising NGR-TNF as taught by Curnis et al for the peptide such as SEEVCWPVAEWYLCNMWGR that inherently binds to the VEGFR-3 as taught by the '416 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Curnis *et al* teach targeted delivery of TNF may enhances its immunotherapeutic properties without less systemic toxicity (See abstract, in particular). The '416 patent teaches that reference peptide is useful as IGF antagonist for inhibiting angiogenesis in cancer (See column 25, lines 44, in particular).

21. Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirohashi *et al* (Mol Pharmacol 53(6): 1068-75, June 1998; PTO 892) in view of US Pat No 6,121,416 (Sept 2000; PTO 892).

The teachings of Hirohashi *et al* have been discussed supra.

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The claimed invention as recited in claim 23 differs from the teachings of the reference only in that the isolated peptide further comprising amino- and carboxy-terminal cysteine residues.

The '416 patent teaches any peptide would have been conformationally stabilized by cyclization such as substituting at amino acids at the N and C terminal cysteines and is well known in the art that a disulfide bond can be formed between the terminal cysteines (See column 23, lines 28-67, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute or add a cysteine residue at both ends (amino- and carboxy-terminal cysteine residues) of a peptide taught by Hirohashi et al to form cyclization as taught by the '416 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to include cysteine residues at the amino- and carboxy-terminal of a peptide because disulfide bond can be formed between the terminal cysteines and cyclization via two terminal cysteines would have been expected to stabilize any peptides as taught by the '416 patent.

22. The isolated peptide consisting of the amino acid sequence CGYWLTIWGC (SEQ ID NO: 35) is free of prior art.
23. No claim is allowed.
24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.
25. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 17, 2004


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